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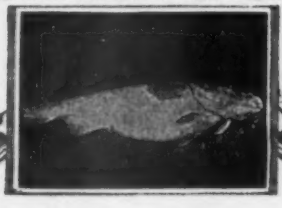

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ENDEMIC GOITRE IN RABBITS

I. Incidence and Characteristics

ALAN M. CHESNEY, M.D., THOMAS A. CLAWSON,[1] M.D., AND BRUCE WEBSTER,[1] M.D.

From the Department of Medicine of the Johns Hopkins Medical School

INTRODUCTION

During the past three years opportunity has been afforded us to observe and study a colony of rabbits in which many members exhibited a tendency to enlargement of the thyroid gland. The condition occurred while the animals were under observation and were being used for the study of experimental syphilis. It was not the intention to produce experimental goitre and the finding was therefore wholly accidental.

Enlargements of the thyroid gland in rabbits, of the degree we have observed in this series of animals, are certainly extremely rare if, indeed, they have been noted before. The common breeds of rabbits obtained from dealers along the Atlantic seaboard will show some variation in size of the thyroid but this variation is relatively slight.

Brown, Pearce and Van Allen (1, 2), in studying a series of 645 apparently normal rabbits, found the maximum weight of the gland to be 1.73 grams, the minimum 0.085 gram, and the arithmetical mean or average 0.2328 gram. Their data form a convenient base line from which to measure the variations that we have observed. Marine (3) has never observed a rabbit thyroid weighing more than 2 grams even in animals obtained from goitrous regions. In the series of rabbits which forms the basis of this communication the thyroid gland often weighed considerably more than the maximum observed by these investigators, so much so that it is possible to say that what we have encountered is an instance of endemic goitre in laboratory rabbits.

[1] Jacques Loeb Fellow in Medicine.

EXPERIMENTAL DATA

As soon as it came to our attention that we were dealing with endemic goitre in our animals we began systematically to weigh the thyroid at autopsy.[2] In only a very few animals was this procedure omitted. We are in a position to report upon a series of 486 animals autopsied between July 30, 1926 and February 29, 1928.

The rabbits were acquired at intervals between September 16, 1924 and January 25, 1928.

Breed. Rabbits of all the common breeds were included in the series studied, but the greys and browns predominated. The great majority were adult males, since these are better adapted than females to the study of experimental syphilis. The main source of supply has been a dealer in York, Pa., with whom we had a contract for supplies at stated intervals. This dealer purchased stock indiscriminately from various rabbitries. Comparatively few rabbits were purchased from local dealers.

Housing. The rabbits were kept in individual cages 12 by 12 by 18 inches, and were housed in rooms with a northern exposure until May 1, 1928, when they were transferred to rooms with southern and eastern, and western exposures, respectively. This change of habitat did not apparently alter the development of goitre. In no instance were the animals exposed directly to sunlight. They had no opportunity to come directly in contact with one another. Shavings were used for bedding and the bedding was renewed weekly.

Diet. The diet consisted of a daily ration of fresh cabbage, a ration of oats three times a week and one of hay once a week. There were some weeks when the hay was omitted. Unfortunately there are no precise data on this point. The animals never received water to drink at any time, it being expected that the liberal ration of cabbage would supply this need. On this diet the animals gained weight.

Intercurrent disease. From time to time some of the animals acquired snuffles and, while we have no precise data as to the incidence of this infection in our animals, it is our opinion that it was not more

[2] The authors desire to express their gratitude for assistance rendered by Dr. Charles R. L. Halley and Dr. Thomas B. Turner in performing some of the autopsies.

prevalent than in other laboratory stocks similarly housed. The same may be said of coccidiosis. We have no data as to the frequency of encephalitis in our animals.

Thyroid weights. All weights recorded in the tables are moist weights. Reference to Table I will show the range of weights of the thyroid gland in the entire series, with the frequency of the various

TABLE I

Range of thyroid weights

WEIGHT	NUMBER OF ANIMALS	WEIGHT	NUMBER OF ANIMALS	WEIGHT	NUMBER OF ANIMALS
grams		*grams*		*grams*	
0.0 –0.5	46	9.01–10.0	3	19.01–20.0	3
0.51–1.0	107	10.01–11.0	7	20.01–22.0	0
1.01–2.0	155	11.01–12.0	5	22.01–23.0	1
2.01–3.0	64	12.01–13.0	3	23.01–30.0	0
3.01–4.0	31	13.01–14.0	2	30.01–31.0	1
4.01–5.0	18	14.01–15.0	0	31.01–34.0	0
5.01–6.0	13	15.01–16.0	0	34.01–35.0	1
6.01–7.0	9	16.01–17.0	1	35.01–36.0	2
7.01–8.0	4	17.01–18.0	0	36.01–42.0	0
8.01–9.0	7	18.01–19.0	2	42.01–43.0	1
Total number of animals examined.....					486

TABLE II

Comparison of thyroid weights in two series of rabbits

	NUMBER OF ANIMALS	MINIMUM	MAXIMUM	AVERAGE	STANDARD DEVIATION	STANDARD ERROR OF AVERAGE
		grams	*grams*	*grams*	± *grams*	± *grams*
Brown, Pearce and Van Allen series.....	644	0.085	1.730	0.2328	0.1475	0.0058
Our series.....	486	0.1–	43.0	2.93	4.6489	0.2109

weight groups. When these figures are compared with those of Brown, Pearce and Van Allen, to which reference has already been made (see Table II), it will be seen that there was a marked tendency in our animals to develop striking enlargements of the thyroid gland. Thus the maximum thyroid weight we have observed was 43 grams as contrasted with 1.73 grams, the maximum observed by the former investigators. The arithmetical mean or average weight in our series

was 2.93, as against 0.2328 gram in Brown's series. A comparison of the frequency distribution of the thyroid weights in the two series shows such a marked difference as to leave no doubt that in our series there was present an almost constant tendency of the glands to increase in size. Dr. Halbert Dunn of the Department of Biometry of the Johns Hopkins School of Hygiene has been kind enough to analyze our data from a statistical standpoint and his analysis shows that the differences in weight of our animals and those of Brown, Pearce and Van Allen cannot possibly be explained upon a basis of chance sampling. The striking difference between the two groups may be simply expressed by calling attention to the fact that of our entire 486 animals 440, or 90 per cent, showed thyroids weighing more than 0.5 gram, which is approximately twice the average thyroid weight encountered by Brown, Pearce and Van Allen, and in 178 or 36 per cent of the animals the thyroid weighed more than 2.0 grams, which is the maximum observed by Marine (3) in rabbits and exceeds Brown's maximum (1.730 grams).

It soon became apparent that time was an important factor in the development of the goitre. The longer the rabbits were kept under observation the greater was the tendency for them to show an increased thyroid weight. This is clearly brought out in Table III and in Figure 1. It will be seen from this table that most of the animals were autopsied within 200 days after the date of acquisition. This is due to the fact that many of our experiments dealing with syphilis in the rabbit terminated within that period, but there were a few experiments which were of such a nature that it was necessary to retain the animals for a much longer period of time, and it was in the animals used in these experiments that goitre was first observed with considerable frequency.

Reference to Table III shows a rather sharp increase in the minimal, maximal, and average weights of thyroids in rabbits autopsied from about the 200th day on. We have not seen a thyroid weighing more than 0.5 gram in rabbits autopsied within the first three weeks after admission to the laboratory, and in most instances under these conditions the gland weighed considerably less than this amount. On the other hand, in animals kept under observation more than 200 days it was rare to find a thyroid weighing under 1.0 gram and many weighed

considerably more than this amount. However it should be noted that even in animals kept under observation for more than 500 days an occasional thyroid was encountered which did not exceed 1.73 grams, the maximum observed by Brown and his co-workers.

Clinical course. Many of the goitres were easily recognized by

TABLE III

Relation of thyroid weight to duration of observation

DURATION OF OBSERVATION	NUMBER OF ANIMAL	THYROID WEIGHTS		
		Minimum	Maximum	Arithmetical mean
days		*grams*	*grams*	*grams*
1– 20	14	0.1	0.5	0.18
21– 40	9	0.1	1.0	0.43
41– 60	17	0.1	1.9	0.86
61– 80	11	0.3	1.5	0.9
81– 100	19	0.1	2.3	1.05
101– 120	37	0.4	3.0	1.47
121– 140	51	0.4	4.2	1.39
141– 160	55	0.1	5.1	1.61
161– 180	45	0.3	5.4	1.73
181– 200	42	0.3	10.6	2.25
201– 220	21	0.7	9.8	3.56
221– 240	23	0.7	6.3	2.28
241– 260	24	0.7	11.7	2.89
261– 280	8	1.5	7.9	3.9
281– 300	11	0.8	12.5	3.32
301– 340	4	1.1	5.0	2.42
341– 380	10	1.2	19.3	5.8
381– 420	17	0.7	11.5	3.97
421– 460	10	1.5	36.0	12.0
461– 500	17	0.8	18.2	6.0
501– 540	12	1.1	22.2	6.77
541– 600	9	1.8	12.8	4.8
601– 700	6	1.2	18.5	6.2
701– 800	7	4.2	43.0	19.5
801–1,000	7	2.8	35.7	11.7

palpation, and the progressive enlargement could be followed clinically (Figs. 2, 3). The time at which it appeared varied greatly. As soon as we knew that we were confronted with a tendency to the development of goitre in our animals, all in-coming rabbits were palpated to exclude the presence of an already existing goitre. We

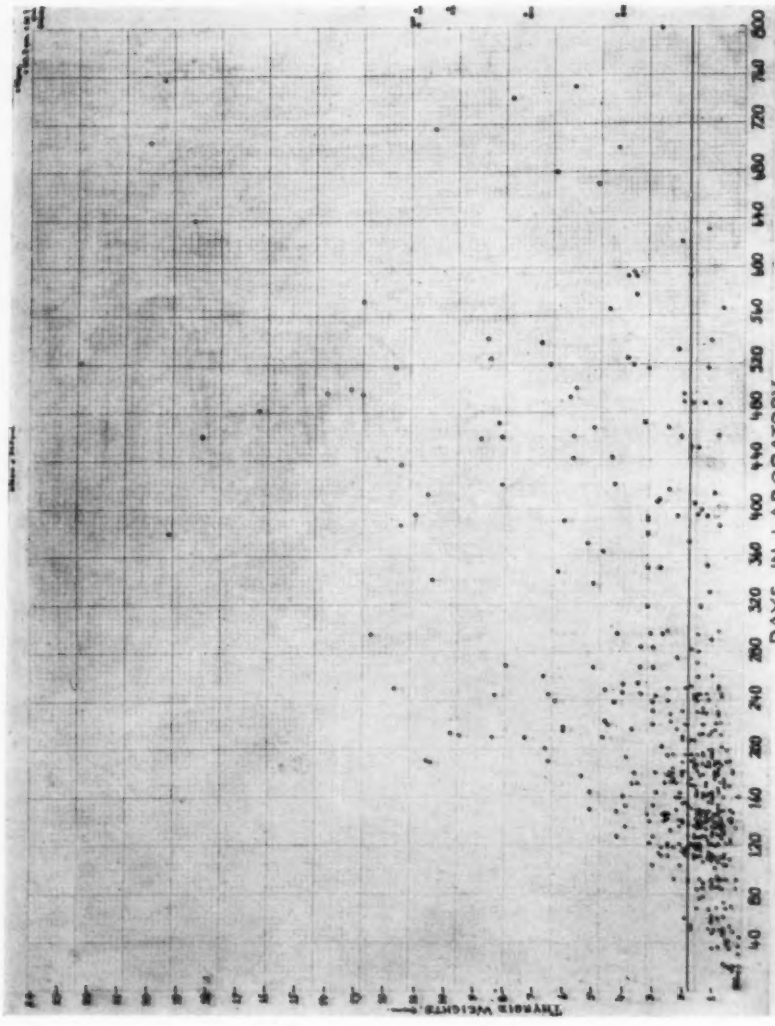

FIG. 1. CHART SHOWING RELATION OF THYROID TO DAYS IN LABORATORY

have never been able to feel the thyroid in any "normal" rabbit examined immediately upon admission to the animal room, nor have we been able to feel it in an old breeding stock to which we had access through the kindness of Dr. Carroll G. Bull of the Johns Hopkins

FIG. 2. RABBIT 1238. PHOTOGRAPH MADE ON THE 389TH DAY OF OBSERVATION

School of Hygiene. We feel justified in concluding, therefore, that the thyroid gland in "normal" rabbits is rarely palpable during life, a statement which is borne out by the figures of Brown and his co-workers.

No significant change in the behavior or general condition of the

animals could be detected when the thyroid became palpable or even after it had attained a large size. If anything, the animals appeared somewhat quieter, but this tendency was not striking as compared with non-goitrous animals. They certainly gained weight. In a few the eyes appeared to be more prominent than usual, even in some instances

FIG. 3. RABBIT 1529

The hair has been clipped to show the neck more clearly

to the extent that it was noticed by lay persons, but this tendency was not uniform and we do not wish to convey the idea that these animals had exophthalmic goitre. There were no significant changes in body temperature. The heart rate in rabbits is too rapid to count without the aid of the galvanometer, and it was impossible to have sufficient

electrocardiograms made to determine whether or not there were any significant changes in the heart rate in those animals in which goitre occurred. There was no tendency to diarrhea except sometimes a few days before death.

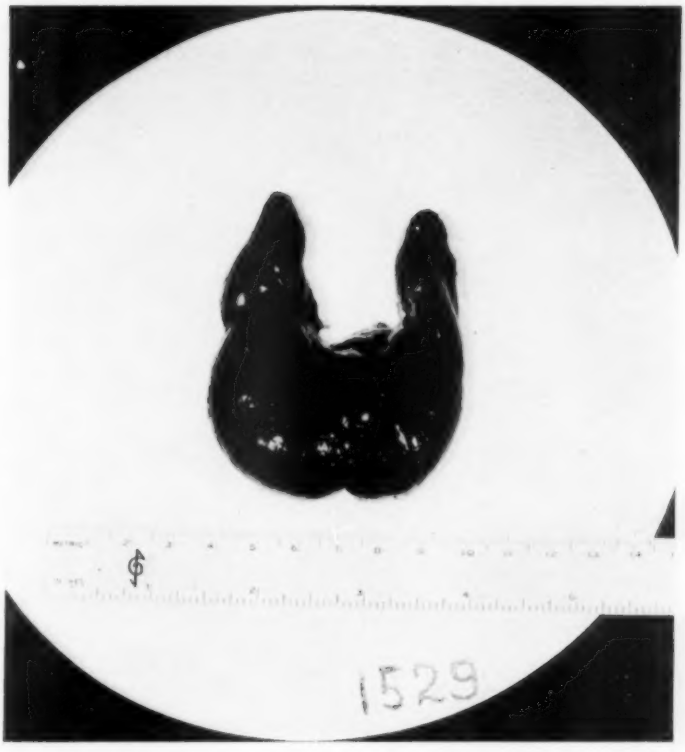

FIG. 4. THYROID OF RABBIT 1529—WEIGHT, 36 GRAMS

PATHOLOGICAL DATA

Most of the animals in the series were sacrificed, but many of those with recognizable goitre were kept under observation until they died a natural death. In some of these last the autopsy revealed condi-

tions such as pneumonia, empyema or colitis, to which the death of the animal could readily be ascribed. There were other goitrous animals, however, in which the autopsy revealed no cause for death whatsoever. Such animals lost weight rapidly during the last few weeks of life and post-mortem examination uniformly revealed a complete absence of body fat, but no gross abnormalities were observed in the organs other than enlargement of the thyroid glands and, to a less extent, of the suprarenal glands.

FIG. 5. THYROID OF RABBIT 1238—WEIGHT, 34.2 GRAMS

The enlarged thyroid at autopsy presented a mottled reddish purple or reddish brown appearance (Figs. 4, 5). The nutrient arteries and veins were enormously enlarged and the gland bled readily on section. The enlargement was always diffusely distributed, both lobes and isthmus being implicated. Very frequently the trachea was almost encircled and many times it was compressed by the gland and its shape altered. In the rabbit exhibited in Figure 2 the tracheal

compression was of sufficient extent to produce stertorous breathing which persisted for weeks and was clearly audible at some distance from the animal's cage.

The microscopic appearance of the enlarged glands was, on the whole, uniform (Figs. 6, 7). There was obvious hyperplasia with no tendency to colloid formation. While some of the follicles contained

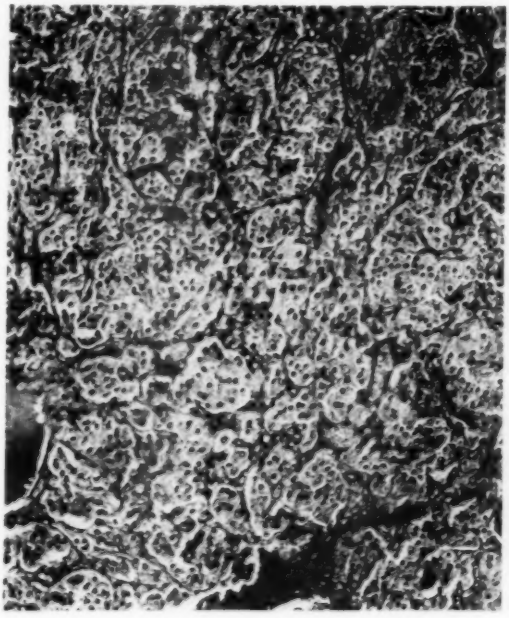

FIG. 6. PHOTOMICROGRAPH OF SECTION OF ENLARGED THYROID

colloid, these were relatively few in number and most of them contained no colloid or amounts much less than one sees in the normal thyroid. It was evident that the increase in size of the gland had been brought about by the formation of many new follicles, or an extension of those already in existence; in other words, it was due to the production of new thyroid acinar cells and not to the formation of colloid or to the accumulation of much new interstitial tissue. The

epithelium was columnar in type and in many of the sections the lumina of the follicles were ill-defined or absent, being filled by the proliferation of epithelial cells. There were no in-foldings of the epithelium such as have been seen in exophthalmic goitre in man.

Some of the sections showed focal accumulations of lymphoid cells, but this finding was not uniform. On the other hand the increased vascularity of the gland was uniformly manifest in the sections, there

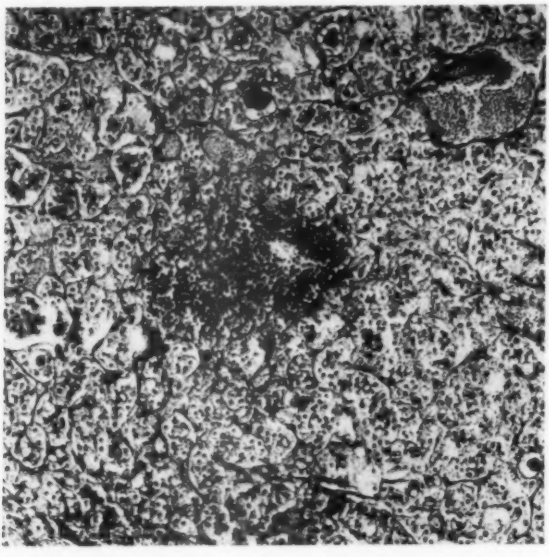

FIG. 7. PHOTOMICROGRAPH OF SECTION OF ENLARGED THYROID
Note lymphocytic infiltration

being many new vessels, some of considerable size. In *summary* it may be said that the appearance of the thyroid microscopically was that of hyperplasia of epithelial elements without a tendency to colloid formation and with marked vascularity and, at times, focal accumulation of lymphoid cells.

The only other abnormality noted at autopsy in the rabbits with goitre was the tendency to enlargement of the suprarenal glands. We

have records of the weights of these organs in 229 animals of the series. In Table IV the suprarenal weights of Brown, Pearce and Van Allen's series of rabbits are shown, together with those of our own rabbits for comparison. This comparison indicates that there was a distinct tendency for the rabbits in our series to show enlargement of the suprarenal glands although the enlargement of these glands was not so great as in the case of the thyroids.

Furthermore, there was observable, in our series, a general tendency for the suprarenals to be larger in those animals in which the thyroid

TABLE IV

Comparison of suprarenal weights of two series of rabbits

	MINIMUM	MAXIMUM	AVERAGE	NUMBER OF ANIMALS
	grams	*grams*	*grams*	
Brown, Pearce and Van Allen series	0.115	1.05	0.3833	645
Our series	0.2	1.8	0.704	229

TABLE V

Relation of thyroid weights to suprarenal weights

NUMBER OF ANIMALS	WEIGHT OF THYROID	MINIMUM	SUPRARENAL WEIGHTS, MAXIMUM	ARITHMETICAL MEAN
	grams	*grams*	*grams*	*grams*
15	0.0 – 0.5	0.2	0.8	0.49
48	0.51– 1.0	0.2	1.2	0.68
71	1.01– 2.0	0.2	1.8	0.68
31	2.01– 3.0	0.4	1.4	0.74
19	3.01– 4.0	0.4	1.25	0.72
45	4.01–36.0	0.4	1.3	0.78

was enlarged, as may be seen by reference to Table V, although this correlation could not be strictly applied. For example, some of the animals with very large goitres had suprarenals within normal limits of size and weight.

No significant alterations in size were observed in the other glands of internal secretion, as determined by inspection.

RELATION OF THE GOITRE TO SYPHILIS

Inasmuch as most of the rabbits in which goitre was observed had been infected with virulent strains of *Treponema pallidum* and had

exhibited manifest syphilitic lesions, it was deemed necessary, as a first step in determining the cause of the goitre, to eliminate syphilis as an etiologic factor. In order to settle this question two series of

TABLE VI

Development of goitre in non-syphilitic rabbits. (Expt. 1, begun Sept. 21, 1926)

RABBIT NUMBER	DAYS OBSERVED	DAY THYROID FIRST FELT	WEIGHT AT DEATH	WEIGHT OF THYROID	WEIGHT OF SUPRARENALS	REMARKS
			grams	*grams*	*grams*	
1527	619	209	2,370	6.5	1.5	Snuffles; sacrificed
1528	457	209	1,800	8.8	0.5	Snuffles; sacrificed
1529	428	160	2,100	36.0	0.9	Snuffles; sacrificed
1531	553	195	2,336	1.2		Sacrificed; broken back
1532	353	195	1,560	1.2		Dead; caseous abscess of bladder wall
1533	618	185	2,370	2.0	1.4	Sacrificed
1534	459	195	1,640	8.1		Dead; no apparent cause
1536	188	160	1,536	10.5	0.5	Dead; no apparent cause

TABLE VII

Development of goitre in non-syphilitic rabbits. (Expt. 2, begun Mar. 1, 1927)

RABBIT NUMBER	DAYS OBSERVED	DAY THYROID FIRST FELT	INITIAL WEIGHT	WEIGHT AT DEATH	WEIGHT OF THYROID	WEIGHT OF SUPRARENALS	REMARKS
			grams	*grams*	*grams*	*grams*	
1743	342	143	2,037	1,900	10.4	1.4	Died; no apparent cause
1744	269	143	2,198	2,100	7.9	0.9	Died; caseous empyema
1745	384	184	2,299	1,200	4.2	0.5	Died; no apparent cause. Lugol's solution for 18 days before death
1746	244	242	2,159	2,560	1.5	0.6	Sacrificed; back broken
1747	450	Not felt	2,775	1,390	0.4	0.8	Died; no apparent cause
1748	241	Not felt	2,186	1,820	1.6	0.7	Sacrificed; severe mange
1749	211	Not felt	2,130	1,400	0.7	0.7	Died; pneumonia
1756	402	Not felt	1,830	1,350	0.4	0.7	Died; no apparent cause
1760	456	Not felt	1,834	1,985	1.0	0.9	Sacrificed
1762	456	Not felt	1,684		2.1	1.4	Sacrificed

rabbits, comprising 8 and 10 head respectively, were set aside and kept under conditions of housing and diet identical with those under which the syphilitic animals that developed goitres were maintained. These

animals were not subjected to any experimental procedures. One of these experiments was begun September 21, 1926, the other March 1, 1927. They were terminated prior to June 15th, 1928. The results are recorded briefly in Tables VI and VII.

Reference to Table VI shows that of the 8 rabbits with which the experiment was begun two died within a year and one died 459 days after the experiment was begun. The others were sacrificed at various times and for various reasons. In 2 of the 3 animals which died "spontaneously," marked enlargements of the thyroid gland were encountered, 8.1 and 10.5 grams respectively; in the other animal the thyroid weighed 1.2 grams, which may be designated a "high normal." Of the 5 animals which were sacrificed, two were moribund at the time and in these the thyroids weighed 8.8 and 36.0 grams, respectively. In the remaining 3 the thyroids weighed 6.5, 2.0 and 1.2 grams, respectively.

Thus, in the 8 animals with which this experiment was begun, marked enlargement of the thyroid developed in 5 during the period of observation. In the remaining 3 animals the thyroid weighed considerably more than the average normal of Brown, Pearce and Van Allen. The enlargement of the thyroid could be detected by clinical examination as early as the 160th day of observation.

The results in the second experiment were less striking, perhaps because it was of shorter duration than the first. Reference to Table VII shows that goitre developed in 3 of the 10 animals, and in 4 others the thyroid weighed between 1.0 and 2.1 grams. In only 3 animals in the series did the gland weigh less than 1.0 gram. That the goitre-producing factor was operative in this series of rabbits cannot be doubted, but it seems equally clear that this factor, whatever it is, was not as effective in this group of animals as in the other.

Inasmuch as not one of these 18 animals was inoculated with syphilis, it is possible to say that syphilitic infection was not necessary to the production of goitre.

DISCUSSION

The foregoing data are sufficient to warrant the conclusion that we have encountered a condition of widespread endemic goitre occurring in rabbits kept under close confinement on a uniform diet and used for

the study of experimental syphilis. Certain features of the disease are worthy of note. First, the variability in incidence should be mentioned. An occasional animal failed entirely to acquire a goitre, while others purchased at the same time, kept under the same conditions of housing and diet and observed just as long, exhibited large goitres. The element of time was found to be a most important one in bringing about the enlargement of the thyroid, but time alone could not be held responsible, since one animal which has been maintained under observation for the longest period of all, nearly 4 years, has as yet failed to show any evidence of goitre.

Observation of selected groups of rabbits kept under identical conditions but not inoculated with syphilis demonstrated that syphilitic infection was not essential to the development of the goitre, although the possibility exists that it may have been a contributing factor. There was no indication that any of the infections to which rabbits are naturally susceptible played an etiologic rôle.

In many instances the enlargement of the thyroid was progressive and the animal subsequently died without any demonstrable cause for death. In these animals the extreme loss of weight was striking. The gross and microscopical appearance of the enlarged thyroids was sufficient to warrant the conclusion that the enlargement was due not to the formation of colloid but to hyperplasia of the cellular elements. In other words, there were many new epithelial cells and these tended to be larger and more columnar in type than those of the normal rabbit. Neither the general behavior of the animals nor the microscopical appearance of the glands would entitle one to say that the condition was similar to Graves' disease in man.

The essential cause of the development of the goitre has not yet been ascertained. That it is related to some special condition obtaining in the quarters in which the animals were kept or in the manner in which they were fed or cared for, can scarcely be doubted, since a similar condition has not been found elsewhere in laboratory rabbits so far as we are aware. It should be stated that the manipulations incident to feeding and cleaning the cages were such that the possibility of transmission of an infectious agent from animal to animal could not be absolutely excluded, even though the rabbits were kept in individual cages.

Experiments are in progress at the present time to determine whether diet or other factors may be responsible for the development of the goitre.

SUMMARY AND CONCLUSIONS

Enlargements of the thyroid gland have been observed in a series of 486 rabbits that have been under observation for varying intervals since September, 1924. The frequency and extent of the condition have been such as to warrant the use of the descriptive term "endemic goitre." Although most of the animals had been used for the study of experimental syphilis, it was possible to demonstrate that syphilitic infection was not essential to the development of the condition. Time was found to be an important factor in its development, however. The gross and microscopical appearance of the glands was that of a hyperplastic thyroid. Many of the animals with enlarged thyroids had also enlarged suprarenal glands. The essential cause for the development of the goitre has not been discovered.

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ENDEMIC GOITRE IN RABBITS

II. Heat Production in Goitrous and Non-Goitrous Animals

BRUCE WEBSTER,[1] M.D., THOMAS A. CLAWSON,[1] M.D. AND ALAN M. CHESNEY, M.D.

From the Department of Medicine of the Johns Hopkins Medical School

INTRODUCTION

In a previous paper (1) the occurrence of spontaneous goitre in a series of laboratory rabbits has been reported. Both the clinical course of the condition and the gross and microscopical appearance of the gland were such as to make it desirable to study the heat production in these animals, in order to obtain a clearer understanding of the nature of the morbid process. This communication deals with the results of such a study. So far as we have been able to determine, heat production has never been studied over a long period of time in either man or animals with simple goitre. Since the condition observed in our animals is probably analogous to that of simple goitre in human beings (2), and since the life span of a rabbit is relatively short compared with that of man, the observations of heat production in goitrous rabbits reported in this paper may perhaps be comparable with those made over longer periods in man with simple goitre.

METHOD

These studies have been carried out by means of Marine's modification of Haldane's open circuit apparatus for measuring the respiratory exchange in rabbits (3).[2] Each observation was of two hours' duration. Frequent blank determinations were made to check the reliability of the apparatus. Owing to the ability of a rabbit to store large quantities of food in its stomach, true fasting conditions are hard to obtain. Accordingly, following Marine's procedure, determinations

[1] Jacques Loeb Fellow in Medicine.

[2] The authors with to thank Dr. David Marine for the loan of the apparatus with which these studies were made.

of heat production were carried out under standard conditions. These were established by placing the animal in a clean cage, without food, 18 to 24 hours before the determination was made. As a rule the animal remained quiet, often sleeping throughout the experiment. If excessive movement occurred, the observation was discarded. The first determination on an individual rabbit frequently gave a higher result than subsequent ones. In all probability this was due to the fact that the animal was unaccustomed to the metabolism chamber and no significance has been attached to these initial determinations. The results are expressed in calories per kilogram per hour, as well as total calories per two-hour period. The former value is spoken of in this paper as the "basal rate," although for reasons cited above the conditions are not, strictly speaking, "basal."

McCann (4) has criticized Marine's observations because of the irregularity of the respiratory quotients and the daily variations in metabolism as measured by gaseous exchange. The variations in respiratory quotients may be due, as McCann suggests (5), to the fact that combustible gases, resulting from the break-down of carbohydrate material in the gut of herbivorous animals, are given off during the determination. If so, this is a factor which is difficult to eliminate. Slight daily variations in metabolism do occur, but on the whole the results obtained by various observers have been reasonably constant, if the standard conditions described above were observed.

HEAT PRODUCTION IN NORMAL RABBITS

Marine (3), who has studied the heat production in many rabbits, states that the normal range is between 2.40 and 2.50 calories per kilogram per hour. In seeking to establish normal values for comparison with the goitrous animals it was deemed important to take into consideration the time that the animal had been in the laboratory, for, as brought out in the previous paper of these series, there was a direct relationship between the size of the thyroid gland and the length of a period during which the animals were under observation and hence exposed to the unknown conditions responsible for the development of the goitre. While it was often several months before the thyroids could be determined by palpation to be enlarged, nevertheless, the weights of the glands at autopsy were such as to convince us that, in

our particular series, the rabbits could not strictly be considered "normal" if determinations were made after the 45th day in the laboratory. Excluding the first determination on each animal, the average heat production of 96 such "normal" rabbits was 2.64 calories per hour per kilogram. In our experience, some apparently healthy animals repeatedly exhibit a basal rate slightly higher than the normal, as given by Marine, while others show a consistently lower rate, over a long period of time. Accordingly, it would appear that, like the human being, each rabbit has its own normal level which should be established before concluding that increases or decreases in heat production have occurred as the result of abnormal conditions. There is, fortunately,

TABLE I

Heat production in normal animals

DAYS IN LABORATORY	NUMBER OF OBSERVATIONS	CALORIES PER KILOGRAM PER HOUR		
		Maximum	Minimum	Average
1–5	22	3.45	2.28	2.83
6–10	8	3.37	2.47	2.84
11–15	31	3.33	2.18	2.77
16–20	6	3.67	2.36	2.81
21–25	7	3.11	1.87	2.52
26–30	7	3.28	1.98	2.53
31–35	8	2.80	1.95	2.42
36–45	5	3.28	2.12	2.39

a tendency for these normal levels to be within comparatively narrow limits.

Table I shows the heat production in a series of normal rabbits, tabulated according to duration in the laboratory.

There was observed a slight but definite tendency for the average basal rate to fall as the period of stay in the laboratory increased. This is shown graphically in Chart I. It may be that this decrease in heat production was brought about by either one or both of the following conditions:

1. The animal becoming accustomed to the metabolism chamber. Repeated observations made on normal animals during a short time period showed that there was a progressive drop during the first two or in some cases three observations, but that thereafter the animal

apparently became accustomed to the chamber and the heat production remained constant. In compiling the above table, the first two observations on each animal have been excluded, thus reducing this factor to a minimum.

2. The possibility of the goitrous process beginning to manifest itself even before the 45th day. McCarrison (6) states that goitre usually develops in susceptible subjects in from 40 to 90 days after exposure to goitrogenous influences.

The question arose as to whether or not changes in weight affected the heat production to any extent. Since results are expressed on

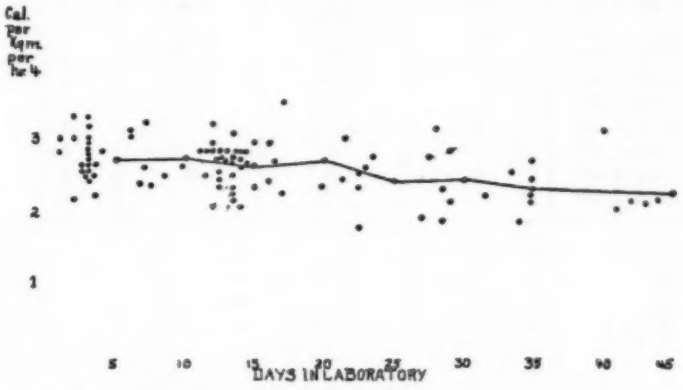

CHART I. HEAT PRODUCTION IN "NORMAL" RABBITS, ARRANGED ACCORDING TO DAYS IN LABORATORY

0 indicates average metabolic rate per time interval

the basis of body-weight, it seemed desirable to consider this factor in setting up normal standards. The only available formula for determining the surface area in rabbits is that of Pfaundler (7) which is as follows:

$$\text{Surface area (sq. cm.)} = 12.0 \times (\text{wt. in kg.})^{\frac{2}{3}}$$

When this formula is applied to rabbits and the surface area calculated for animals weighing from 1,400 to 2,800 grams, it is found that the surface area varies almost directly with the weight of the animal. The difference in the proportional increases of the two measurements

TABLE II

Heat production in normal animals

WEIGHT RANGE	NUMBER OF OBSERVATIONS	CALORIES PER KILOGRAM PER HOUR		
		Maximum	Minimum	Average
grams				
1,401–1,500	1	2.58		2.58
1,501–1,600				
1,601–1,700	4	2.96	2.35	2.55
1,701–1,800	14	3.28	2.18	2.82
1,801–1,900	8	3.47	2.32	2.98
1,901–2,000	12	3.16	2.28	2.77
2,001–2,100	10	3.25	2.62	2.87
2,101–2,200	13	3.45	2.39	2.76
2,201–2,300	11	2.85	1.87	2.62
2,301–2,400	3	3.23	2.05	2.59
2,401–2,500	1	2.37		2.37
2,501–2,600	1	2.46		2.46
2,601–2,700	2	2.11	2.08	2.09
2,701–2,800	1	2.28		2.28

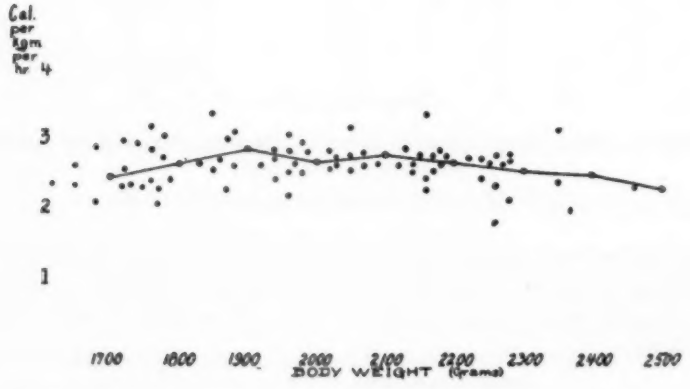

CHART II. HEAT PRODUCTION IN "NORMAL" RABBITS, ARRANGED ACCORDING TO BODY-WEIGHT

0 indicates average metabolic rate for each weight group

is so slight, within the stated limits, that it is possible to ignore the determination of surface area by the formula cited above and to express all observations on the basis of weight alone. Table II, based on 81 observations tabulated according to weight ranges, shows that a wide variation in body weight (1,400 to 2,800 grams) can occur with only moderate change in the average basal rate. This is shown graphically in Chart II.

The same fact may be demonstrated when repeated determinations of heat production are made upon an animal showing marked changes in weight. Protocol 1 illustrates such an instance.

PROTOCOL 1

Rabbit 1532

DATE	DAYS IN LABORATORY	WEIGHT	O_2, 2 HOURS	CO_2, 2 HOURS	R.Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KILOGRAM PER HOUR	
1927			*grams*	*grams*				
March 1.....	161	2,740	2.94	3.46	0.85	10.76	1.83	
March 11.....	171	2,661	3.15	3.52	0.81	10.58	1.99	
March 24.....	184	2,476	3.02	3.52	0.84	10.23	2.07	
April 27.....	218	2,552	3.22	3.52	0.79	10.81	2.12	
May 4.....	225	2,302	3.50	3.77	0.78	11.73	2.55	
May 10.....	231	2,242	3.25	3.52	0.78	10.84	2.42	
May 31.....	252	2,192	3.10	3.59	0.84	10.51	2.40	
July 6.....	288	2,129	2.60	3.39	0.94	9.03	2.12	
September 9.....	353							Death. Weight of thyroid 1.2 grams

From this protocol, it is apparent that a variation even as much as several hundred grams in body-weight can occur without a marked alteration in heat production.

It can be readily seen that one can not fix a definite figure as the normal level of heat production in the rabbit and call all variations from that figure "abnormal." Charts I and II however show that most of the normal values (actually 68 per cent) fall within the limits of 2.3 and 2.9 calories per kilogram per hour.

Young normal animals, not fully grown, show slightly higher basal

rates than more mature ones. No striking difference has been noted in the heat production in various breeds of rabbits. It is fully recognized that the rabbit is not an ideal animal for the determination of heat production, and that the values cited above for "normal" animals, are not necessarily to be taken as standards for that species, particularly when the age of the animal is not known. However, it is thought that they represent a base line for comparison with the other rabbits in which goitres developed, in the same laboratory.

PROTOCOL 2

Rabbit 1529

DATE	DAYS IN LABORATORY	WEIGHT	O_2, 2 HOURS	CO_2, 2 HOURS	R.Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KILOGRAM PER HOUR	
1927			*grams*	*grams*				
February 28.....	161	2,793	2.54	3.11	0.89	8.70	1.56	Thyroid very large
March 11.....	172	2,548	2.39	2.67	0.81	8.03	1.58	
March 23.....	184	2,434	2.58	2.87	0.81	8.65	1.78	
April 26.....	218	2,523	2.92	3.37	0.84	9.77	1.94	
May 10.....	233	2,435	2.88	2.91	0.73	9.47	1.95	
June 28.....	282	2,583	2.76	2.96	0.79	9.13	1.77	
July 7.....	289	2,320	2.24	2.41	0.78	7.47	1.61	
November 23....	428							Death. Weight of thyroid 36 grams

HEAT PRODUCTION IN RABBITS WITH GOITRE

Heat production was studied in 45 rabbits with goitre recognized by clinical examination. From two to twenty observations were made on each animal. In some instances the goitre had been present for several months when the determinations were begun; in others determinations were made prior and subsequent to the onset of enlargement of the gland. While there were variations in findings in different animals, in general it may be stated that those with goitre tended constantly to show diminished heat production.

Table III, based on 221 observations, shows the average heat production in the goitrous animals, tabulated according to time periods.

The average basal rate in this series was 2.20 calories per kilogram per hour. Compared with the average figure of 2.64 calories per kilogram per hour for the non-goitrous animals, this represents a decrease of 16.6 per cent. Since this figure is based on all observations made on animals with clinically detectable goitre, it does not give a true conception of the extent to which heat production is depressed in rabbits with a very large thyroid gland. Protocol 2 is that of a rabbit with a

TABLE III

Heat production in goitrous rabbits

DAYS IN LABORATORY	NUMBER OF OBSERVATIONS	CALORIES PER KILOGRAM PER HOUR		
		Maximum	Minimum	Average
51–100	27	2.85	2.90	2.14
101–150	13	2.63	1.73	2.14
151–200	29	3.27	1.56	2.23
201–250	39	3.68	1.70	2.41
251–300	18	3.42	1.60	2.43
301–350	10	3.11	1.88	2.40
351–400	8	2.49	1.53	1.99
401–450	9	3.24	1.83	2.34
451–500	8	2.85	1.96	2.24
501–550	14	3.29	1.86	2.42
551–600	7	2.40	1.68	1.74
601–650	7	2.76	1.99	2.41
651–750	2	2.06	1.90	1.98
751–850	6	3.56	1.90	2.33
851–950	8	2.80	1.83	2.17
951–1,050	6	2.57	1.78	1.95

thyroid gland which weighed 36.6 grams. Here the basal rate, studied over a period of four months, was well below the average level.

By reviewing the protocols of many animals, it became apparent that the degree of depression of heat production paralleled, to some extent, the degree of enlargement of the thyroid gland. As the gland has to be much enlarged before it is palpable in the living animal, it is impossible to detect clinically the exact date of onset of the goitrous process. As pointed out in the previous communication, animals that have remained in the laboratory for 150 days or more almost invariably show enlargement of the thyroid gland at autopsy. In many animals this begins at even an earlier date. From Table III,

it can be seen that, as early as the 50th to 100th day period, the depression in heat production is already apparent.

Comparisons of basal rate can best be made in animals of the same weight, if the ages are unknown, as was the case in most of our animals. Table IV shows the heat production in goitrous rabbits, arranged according to body-weight, compared with that of "normal" rabbits. Chart III shows graphically the degree of depression of

TABLE IV

Comparison of heat production in rabbits with and without goitre. Arranged according to body-weight

WEIGHT RANGE	"NORMAL" RABBITS				GOITROUS RABBITS			
	Number of observations	Calories per Kilogram per Hour			Number of observations	Calories per Kilogram per Hour		
		Maximum	Minimum	Average		Maximum	Minimum	Average
grams								
1,601–1,700	4	2.96	2.35	2.55				
1,701–1,800	14	3.28	2.18	2.82				
1,801–1,900	8	3.47	2.32	2.98				
1,901–2,000	12	3.16	2.28	2.77	12	3.24	1.68	2.46
2,001–2,100	10	3.25	2.62	2.87	12	3.27	1.78	2.33
2,101–2,200	13	3.45	2.39	2.76	20	2.76	1.83	2.23
2,201–2,300	11	2.85	1.87	2.62	29	3.42	1.90	2.38
2,301–2,400	3	3.23	2.05	2.59	22	3.27	1.61	2.28
2,401–2,500	1	2.37		2.37	33	2.77	1.70	2.15
2,501–2,600	1	2.46		2.46	24	2.82	1.53	2.17
2,601–2,700	2	2.11	2.08	2.09	16	2.40	1.60	2.00
2,701–2,800	1	2.28		2.28	12	3.17	1.56	2.13
2,801–2,900					7	2.25	1.77	1.98
2,901–3,000					4	2.05	1.60	1.98
3,001–3,100					3	2.08	1.90	1.99

heat production in the goitrous animals, as compared with the non-goitrous ones, of the same body-weight.

During the course of this investigation, it was observed that some animals with goitre showed an increase in heat production just prior to death. Basal rates were determined in 14 rabbits during a period within two weeks of death. Nine of the animals showed a definite rise in the metabolic rate which was too great to be accounted for by mere loss in body-weight. Of these nine, only two revealed, at

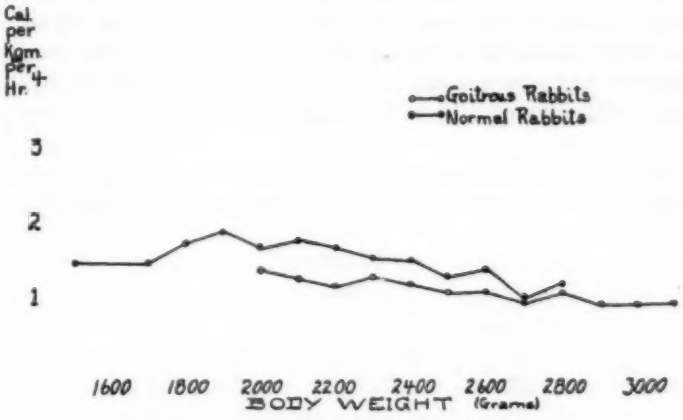

CHART III. HEAT PRODUCTION IN GOITROUS RABBITS COMPARED WITH THAT OF "NORMAL" ANIMALS OF THE SAME BODY-WEIGHT

PROTOCOL 3

Rabbit 1527

DATE	DAYS IN LABORATORY	WEIGHT	O_2, 2 HOURS	CO_2, 2 HOURS	R.Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KILOGRAM PER HOUR	
1927			*grams*	*grams*				
March 3.....	163	2,389	3.47	3.97	0.83	11.76	2.46	
March 12.....	172	2,234	3.09	3.03	0.71	10.12	2.27	
March 23.....	183	2,201	2.58	3.40	0.95	9.02	2.05	
April 26.....	217	2,289	3.19	3.89	0.88	10.94	2.39	
May 26.....	245	2,270	2.79	2.87	0.75	9.22	2.03	
June 30.....	277	2,238	2.70	2.98	0.80	9.05	2.02	
December 14.....	461	2,394	2.78	3.13	0.81	9.37	1.96	
1928								
January 24.....	502	2,439	2.75	2.80	0.74	9.08	1.86	
February 10.....	519	2,180	2.83	3.92	0.97	9.94	2.28	
March 1.....	539							Alive and well. Thyroid palpable.

autopsy, any evidence of a terminal infection which might account for an increase in the basal rate. The average basal rate during the last thirty days of life in these animals was 2.81 calories per hour per kilogram, while the average rate, in the same animals, during a period from 70 to 100 days before death was 2.27, a difference of 19.2 per cent.

Observations of heat production were made on a number of goitrous animals over a period of one year. Provided there was no great

PROTOCOL 4

Rabbit 1531

DATE	DAYS IN LABORATORY	WEIGHT	O_2, 2 HOURS	CO_2, 2 HOURS	R.Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KILOGRAM PER HOUR	
1927			*grams*	*grams*				
March 3	126	2,770	3.43	3.55	0.75	11.36	2.05	
March 11	134	2,635	3.04	3.15	0.76	10.10	1.92	
March 24	147	2,633	2.79	3.53	0.92	9.63	1.83	
April 27	181	2,300	3.04	3.91	0.90	10.81	2.35	
May 4	188	2,313	2.89	3.28	0.82	9.75	2.11	
May 10	194	2,289	2.72	2.82	0.73	9.02	1.97	
May 27	211	2,352	3.16	3.90	0.90	10.86	2.31	
July 8	253	2,354	2.48	2.98	0.87	8.51	1.81	
December 13	411	2,883	3.30	3.75	0.83	11.15	1.93	
1928								
January 20	449	2,927	3.43	4.60	0.97	12.01	2.05	
February 17	477	2,610	3.48	3.75	0.78	11.85	2.27	
March 19	506	2,336	3.31	3.57	0.78	11.09	2.37	
March 19	506							Animal alive and well. Thyroid palpable

variation in the size of the goitre, the basal rate remained practically constant over this time period. Protocols 3 and 4 have been selected to illustrate this point.

During the course of these studies it was recognized that this method of comparing the heat production in two different groups of animals, goitrous and non-goitrous, has its limitations and that it was desirable to obtain data upon individual animals before and after the develop-

ment of goitre. Owing to an interruption in the studies and the death of several animals set aside for this purpose, this attempt was only partially successful. The majority of animals, however, showed a gradual depression in metabolic rate with the onset of clinically recognizable goitre. In a few cases, this change was not detected.

DISCUSSION

The foregoing observations on heat production in "normal" rabbits, while not put forward as standard values, afford a basis for comparison with the findings obtained in the goitrous animals. It is clear that the heat production in the goitrous rabbits in our series was below that of "normal" animals. This fact was more noticeable when the records of individual rabbits were studied. There was apparent an inverse relationship between the size of the gland and the metabolic rate. Decrease in heat production has likewise been found, by other observers (8, 9) in human beings in whom "simple" goitre has developed, so that the latter condition and that which we have observed in rabbits are analogous in this respect. In the light of our present knowledge of thyroid function this finding suggests a state of lowered activity on the part of the gland in the goitrous rabbits.

The interpretation of an increase in the metabolic rate in some goitrous rabbits a few weeks prior to death is difficult. Plummer (10) and others have shown that symptoms of hyperthyroidism may develop in human beings with simple goitre even after years of apparent quiescence. It is not beyond the realm of possibility that in these animals a similar transition occurred. The extreme loss of weight in some of these animals was striking, and this, together with the increased metabolic rate and the absence of any demonstrable cause of death, make one suspect that a fundamental change may have occurred in the function of the thyroid gland in these particular animals.

SUMMARY

1. Heat production was studied in 96 "normal" rabbits. The average metabolic rate in these animals was found to be 2.64 calories per kilogram per hour. Most values were found to fall within the limits of 2.3 and 2.9 calories per kilogram per hour.

2. Wide variation in body-weight occurred without appreciably altering the basal rate.

3. Studies were made of the heat production of 45 goitrous rabbits. In these animals the average heat production was 16.6 per cent lower than in "normal" rabbits.

4. Rabbits with the largest goitres showed the greatest depression in metabolic rate.

5. Heat production in individual goitrous animals was practically constant over a period of one year provided there was no great change in the size of the gland.

6. Certain animals, for which no cause of death could be found, showed an average increase of approximately 20 per cent in their metabolic rate during a period within two weeks of death.

The authors wish to acknowledge their indebtedness to George A. Harrop and to Dr. Wm. a. Perlzweig for many helpful suggestions.

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ENDEMIC GOITRE IN RABBITS

III. Effect of Administration of Iodine

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In the previous papers in this series (1, 2) the occurrence of endemic hyperplastic goitre in laboratory rabbits has been reported, together with observations upon the heat production in these goitrous animals compared with a series of "normal" controls. The average heat production in the animals with goitre was 16.6 per cent lower than in non-goitrous animals of the same relative weight. The thyroid glands of the goitrous animals presented the typical picture of hyperplastic, parenchymatous goitre (Fig. 2). These findings suggested that the goitre observed in our rabbits was analogous to simple goitre in man.

The comparatively large numbers of goitrous animals at our disposal offered an unusual opportunity to study the effect of the administration of iodine in this condition. The present communication deals with the results of such a study. Observations have been made upon (*a*) the clinical condition of the animal; (*b*) the heat production and (*c*) the histological structure of the gland following the administration of iodine.

Marine, Deutch and Cipra (3) have recently suggested that the temporary fall in heat production after the administration of large doses of iodine is not specific for Graves' disease, and should occur in all animals and in all those conditions in man in which there is a deficient iodine store associated with thyroid hyperplasia. They base this idea on Marine's theory that the lowering of basal rate is brought about by the outpouring of colloid and the consequent temporary occlusion of the peri-alveolar lymphatics, resulting in diminished absorption of thyroid hormone into the circulation. In their paper they call attention to the desirability of studying the effect on the heat

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production following the administration of iodine to animals with definitely hyperplastic goitres. Since our rabbits exhibited this condi-

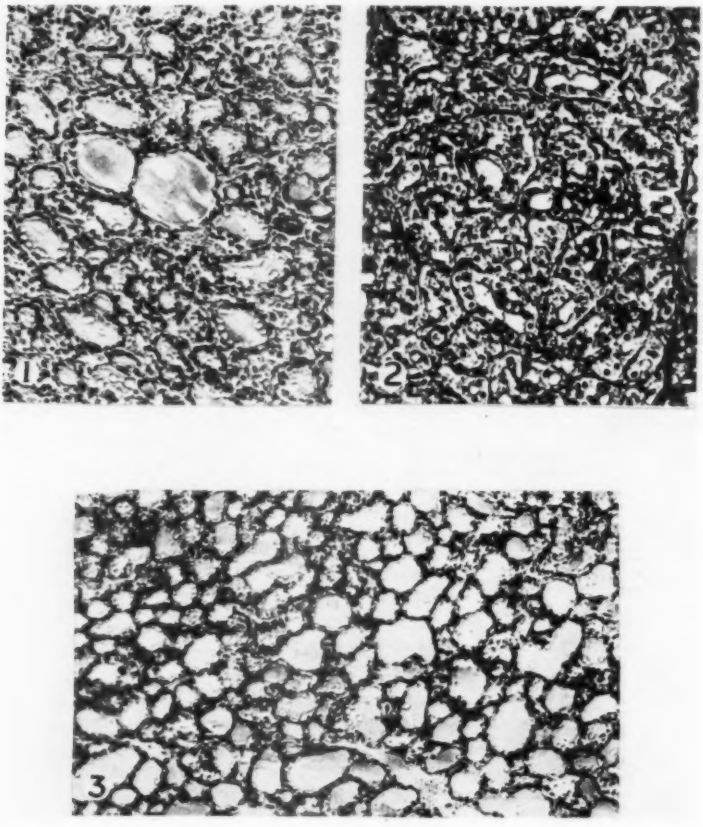


FIG. 1. SECTION FROM THYROID GLAND OF NORMAL RABBIT (× 130)
FIG. 2. SECTION OF HYPERPLASTIC GLAND FROM RABBIT WITH LARGE GOITRE (× 130)
FIG. 3. SECTION FROM THE THYROID GLAND OF A NORMAL RABBIT (NO. 2036) AFTER THE ADMINISTRATION OF IODINE FOR THIRTY DAYS (× 105)

tion to a marked degree, the opportunity was afforded us to perform such an experiment.

EXPERIMENTAL

Heat production was studied in a series of normal and goitrous rabbits before and after the administration of iodine. These determinations were made as in the previous studies (2). Experiments

TABLE I

The effect of iodine on heat production in normal rabbits

	RABBIT 2038	RABBIT 2037	RABBIT 2036	RABBIT 2083	RABBIT 2061	RABBIT 2060
Metabolism before iodine administration. Total calories per 2-hour period.						
Number of readings	3	4	3	3	4	3
Maximum	12.60	13.18	12.66	12.44	10.26	11.32
Minimum	12.17	12.88	11.78	12.04	10.14	10.80
Average	12.25	12.96	11.94	12.20	10.18	11.04
Metabolism after iodine administration (Lugol's solution 0.06 cc. daily). Total calories per 2-hour period.						
1st day		11.64		9.68	9.36	
2nd day	11.56		10.63			9.48
3rd day		10.93		9.20	8.36	
4th day	9.96					9.42
5th day		11.12	12.16	10.92		
6th day	10.34				10.42	*
7th day			12.32			
8th day	10.68	10.88		10.64	10.80	
10th day			11.96		11.06	
11th day	10.86	10.80		11.08		
13th day		11.20			12.26	
14th day	10.88		11.94	11.80		
15th day		11.32			12.38	
30th day	8.68	12.44	11.22	12.00	10.12	

* Broken back; animal sacrificed.

during which the animal was restless and moved about were discarded. The "normal" rabbits used had all been in the laboratory for less than ten days. As soon as satisfactory levels of heat production had been established in these two series of animals, iodine, in the form of Lugol's solution, was administered orally in doses of 0.06 cc. This was placed

in the back of the throat with a medicine dropper. Heat production was studied at intervals until death occurred or no further change took place. In the latter case the animal was then sacrificed and a routine autopsy performed.

EFFECT OF IODINE ON NORMAL RABBITS

Marine, Deutch and Cipra (3) have studied the effect of iodine in large doses on the heat production of eighteen normal rabbits. They report a drop in the metabolic rate in five animals, a slight rise in two, and no appreciable change in the remaining eleven. Examination of their protocols reveals the fact that none of these changes were of a very marked degree. They were unable to correlate, in this series, the histological picture before the administration of iodine with the response to that drug.

Although these results might be considered as a control for similar studies on our goitrous animals, we repeated essentially the same experiment on a group of six "normal" rabbits. Table I shows the results of this experiment. In all 6 cases a decrease in the metabolic rate occurred within forty-eight hours after the first dose of Lugol's solution was given. This reached its maximum degree of depression on the third or fourth day. After that period there was a tendency to a return to the normal level. At the end of two weeks' administration of iodine, three rabbits still showed some lowering of the metabolic rate; one had attained its average normal level and one had appreciably exceeded this level. After one month the metabolism of three animals had returned practically to the normal level, while two still showed a definite depression. The daily dose of Lugol's solution (0.06 cc.) was continued until the animals were sacrificed.

Clinically, no change could be observed in the animals during the period of iodine administration. Three rabbits gained in weight, while three showed a slight loss. One animal (No. 2060) sustained a broken back and had to be killed after five days' observations. The remaining five were sacrificed at the end of the experiment. In none of these animals was the thyroid weight above 0.35 grams, a figure well below the maximum normal of Brown, Pearce and Van Allen (4).

Grossly, the thyroid glands were normal in appearance; microscopical sections showed every acinus distended with fresh-looking colloid material (Fig. 3). This was evenly distributed throughout the whole gland. There was no evidence of hyperplasia in any of the sections. The epithelium was of a low cuboidal type, often almost of the "pavement" variety. The number of colloid cells greatly exceeded the number of chief cells. There was no increase in vascularity.

EFFECT OF IODINE ON GOITROUS RABBITS

The effect of the administration of iodine was observed in ten goitrous rabbits. As far as possible, animals with very large thyroid glands were chosen for this experiment, although in one or two instances we were forced to use those with only moderate thyroid enlargement. The behavior of the animals following the administration of Lugol's solution was strikingly uniform as regards their general condition, heat production and alterations in the microscopical appearance of the thyroid.

Clinically, the effect of iodine on these rabbits was remarkable. Within forty-eight hours after the first dose they changed from quiet, rather sluggish animals to alert, hyperactive ones. They began to lose weight rapidly and became extremely emaciated. The first rabbit (No. 1276) died three days after the initial dose of iodine. The experiment was repeated on another rabbit (No. 1615) with similar results, except that it died on the seventh day of iodine administration. Reference to the accompanying protocols will show that essentially the same thing occurred in each of the animals of this series. In every instance in which the animal survived the iodine administration for more than one week, a decrease in the size of the goitre was noted. In none of the rabbits dying after iodine administration was the cause of death revealed at autopsy. Extreme emaciation was the striking feature, the subcutaneous fat being completely absent. Cardiac hypertrophy was noted in only one animal. The thyroid glands were of a firm consistence and dark brown in color.

The effect on the heat production of the administration of iodine to the goitrous animals was striking. In every instance the metabolic rate began to rise within three days after the first dose of Lugol's

solution. In most cases this increase progressed steadily until death occurred. The greatest rise was obtained in animal No. 1843 in which the metabolic rate rose from 2.58 (the average during the control period) to 5.97 calories per kilogram per hour, an increase of 131 per cent. The average maximum increase was approximately 98 per cent. Reference to the accompanying protocols will show the details of these increases in metabolism. During the course of these experiments it was observed that animals with moderate thyroid enlargement withstood the effect of iodine administration better than those with very large goitres. Protocols 7 and 9 were those of rabbits with only slight enlargement. Rabbit 1747 (Protocol 7) lived for 50 days under iodine administration. The loss in weight was gradual and the elevation of metabolism was not extreme. Rabbit 1842 in which the thyroid gland was barely palpable (Protocol 9) was the only one of the series to survive the experiment. In this case, the increase in heat production was not great and occurred gradually, reaching its maximum level in approximately 35 days, after which there was a slow return to a level slightly above the previous subnormal one. In spite of the discontinuation of iodine, the metabolic rate was still elevated to a slight degree four weeks after the last dose had been given. Animals with very large goitres (Protocols 1, 2, 3 and 6) tended to show a more rapid increase in metabolism and died sooner than those with moderate thyroid enlargement. Protocols 6 and 8 show a preliminary decrease in the metabolic rate following the administration of the first dose of iodine, with a subsequent rise.

An effort was made to meet the increased caloric requirement by doubling the diet, but the weight loss continued. Although Lugol's solution in the dosage used (0.06 cc.) had not been injurious to normal rabbits, this dose was reduced to 0.03 cc. in rabbit 1921 in the hope that the increase in metabolism would be less rapid. However, the same rise occurred as when the larger doses were given.

One animal (No. 1290), with a moderately enlarged thyroid, was sent to Dr. David Marine for similar study. We are indebted to him for the data included in Protocol 10. The results agree essentially with our own observations.

PROTOCOL 1

Rabbit 1276. Thyroid gland very markedly enlarged

DATE (1927)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
December 6	2.97	2.06	12.23
December 9	2.80	2.08	11.64
December 13	2.85	1.90	10.82
December 17	Lugol's solution 0.06 cc. daily		
December 19	2.36	3.33	15.71
December 21	1.90 Death. Thyroid weight 10.4 grams		

PROTOCOL 2

Rabbit 1615. Thyroid gland much enlarged

DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
January 6	2.44	2.15	10.49
January 9	2.39	2.06	9.85
January 11	2.25	2.26	10.17
January 14	2.48	2.00	9.92
January 15	Lugol's solution 0.06 cc. daily		
January 18	1.95	3.86	15.05
January 20	1.85	4.08	15.10
January 22	1.65 Death. Thyroid weight 10.6 grams		

PROTOCOL 3

Rabbit 1493. Thyroid gland much enlarged

DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
February 23	2.10	2.40	10.08
March 2	2.25	2.30	10.34
March 14	2.00	2.25	9.00
March 15	2.07	2.10	8.70
March 16	Lugol's solution 0.06 cc. daily		
March 19	1.61	3.64	11.72
March 21	1.58	3.55	11.20
March 23	1.31 Death. Thyroid weight 7.0 grams		

PROTOCOL 4

Rabbit 1745. Thyroid gland greatly enlarged

DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
January 19	2.62	2.45	12.82
January 28	2.61	2.40	12.53
February 1	2.60	2.42	12.58
February 27	2.53	2.49	12.59
February 29	Lugol's solution 0.06 cc. daily		
March 2	2.05	3.82	15.66
March 6	1.70	5.14	17.47
March 12	1.46	4.73	13.81
March 16	1.43	4.74	13.55
March 19	1.20 Death. Thyroid weight 4.2 grams		

PROTOCOL 5

Rabbit 1843. Thyroid gland moderately enlarged

DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
February 3	1.83	2.80	10.20
February 9	2.08	2.52	10.48
February 19	2.00	2.44	9.76
February 29	Lugol's solution 0.06 cc. daily		
March 2	1.53	5.97	18.27
March 6	1.27	4.34	11.02
March 9	1.16	3.65	8.47
March 11	1.07 Death. Thyroid weight 1.4 grams		

PROTOCOL 6

Rabbit 1921. Thyroid gland much enlarged

DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
May 6	2.24	2.40	10.74
May 7	2.08	2.44	10.15
May 8	2.03	2.56	10.39
May 13	Lugol's solution 0.03 cc. daily		
May 14	1.96	2.51	9.84
May 16	1.84	3.31	12.18
May 18	1.68	4.02	13.50
May 21	1.38	4.65	12.81
May 22	Death. Thyroid weight 7.3 grams		

PROTOCOL 7

Rabbit 1747. Thyroid gland only slightly enlarged

DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
March 10	2.56	2.14	10.95
March 14	2.43	2.24	10.88
March 28	2.42	2.12	10.26
April 2	2.23	2.22	9.90
April 3	Lugol's solution 0.06 cc. daily		
April 5	2.32	2.66	12.34
April 10	2.04	2.04	11.58
April 12	2.02	3.08	12.44
April 16	1.86	4.13	15.36
April 21	1.85	3.37	12.46
April 24	1.79	3.52	12.60
May 2	1.91	3.75	14.30
May 8	1.95	3.73	14.54
May 12	1.85	3.77	13.94
May 19	1.39	3.94	10.94
May 23	Death. Thyroid weight 0.4 grams		

PROTOCOL 8

Rabbit 1654. Thyroid gland moderately enlarged

DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
May 10	2.63	2.12	11.14
May 11	2.60	2.06	10.72
May 12	2.59	2.04	10.56
May 13	Lugol's solution 0.06 cc. daily		
May 14	2.52	1.94	9.76
May 16	2.49	2.62	13.04
May 18	2.37	2.67	12.64
May 22	2.14	3.58	15.32
May 24	2.04	3.64	14.84
May 26	1.94	4.57	17.72
May 29	1.84	3.87	14.24
June 1	Death. Thyroid weight 2 grams		

PROTOCOL 9

Rabbit 1842. Thyroid gland barely palpable

DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
January 18	2.42	1.75	8.46
January 25	2.51	1.74	8.72
January 26	2.50	1.70	8.50
January 28	Lugol's solution 0.06 cc. daily		
February 1	2.25	2.66	11.96
February 6	2.05	2.71	11.11
February 11	2.08	3.40	14.14
February 20	1.94	3.10	12.02
February 27	1.98	3.68	14.57
March 3	2.18	3.64	15.86
March 12	1.91	3.25	12.40
March 16	2.00	2.97	11.88
March 26	1.91	3.27	12.48
April 3	1.94	2.35	9.11
April 10	1.90	2.64	10.03
April 20	1.93	2.46	9.48
April 23	Lugol's solution discontinued		
May 2	2.15	2.79	11.98
May 12	2.27	2.94	13.34
May 19	2.27	2.49	11.30
May 20	Thyroid barely palpable		

PROTOCOL 10

Rabbit 1290. Thyroid gland moderately enlarged

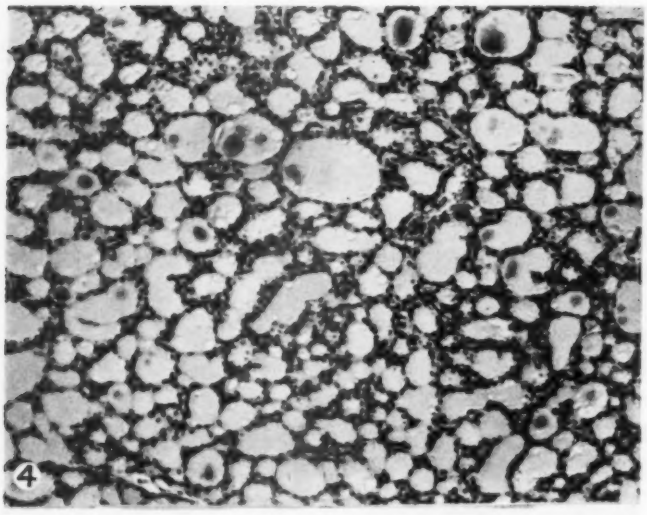
DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
April 3	2.63	1.94	10.19
April 5	2.67	1.94	10.38
April 7	2.64	1.99	10.53
April 10	2.64	1.86	9.83
April 12	2.66	1.91	10.16
April 14	2.63	1.86	9.76
April 16	2.63	1.91	10.04
April 16	KI 25 mgm. intraperitoneally		
April 17	2.65	2.16	11.45
April 17	KI 25 mgm. intraperitoneally		
April 18	2.53	2.36	11.98
April 18	KI 25 mgm. intraperitoneally		

PROTOCOL 10—*continued*

DATE (1928)	BODY-WEIGHT	CALORIES PER KILOGRAM PER HOUR	TOTAL CALORIES PER 2-HOUR PERIOD
	kgm.		
April 19	2.45	2.96	14.49
April 20	2.41	3.25	15.67
April 21	2.35	3.27	15.40
April 23	2.22	4.04	17.95
April 24	2.17	4.00	17.37
April 25	2.18	3.85	16.77
April 26	2.13	4.12	17.52
April 27	2.05	4.02	16.45
April 28	2.00	4.15	16.60
April 30	2.02	3.91	15.82
May 2	1.91	3.83	14.63
May 7	1.69	4.15	14.05
May 9	1.63	3.87	12.61
May 11	Death. Thyroid weight 4.48 grams		

THE data contained in this protocol were supplied by Dr. David Marine.

Microscopical sections of the thyroid glands of these animals revealed hyperplastic goitres in various stages of involution. The degree of involution was directly proportional to the period over which iodine was administered before death. In every case there was apparently an attempt at a return to colloid goitre (Figs. 4, 5). In many acini what appeared to be newly-formed colloid could be seen around a small central mass of apparently older material. When compared with other hyperplastic glands from animals that had not received iodine, the change was striking. The amount of colloid was greatly increased. This was laid down unevenly and the acini were irregular in size. In the glands showing the greatest degree of involution the alveolar epithelium tended to be reduced in height. This tendency was observed by Marine and Lenhart many years ago (5). There were numerous localized, apparently encapsulated areas of colloid, resembling the colloid adenomata found in the human thyroid after hyperinvolution has taken place. Figure 6 shows one of these "adenomata." In one gland (Rabbit 1921) areas of persistent hyperplasia were the remarkable feature. In the greater portion of this gland involution had occurred in the normal way. There were, however, scattered areas of hypoinvolution, which apparently showed no



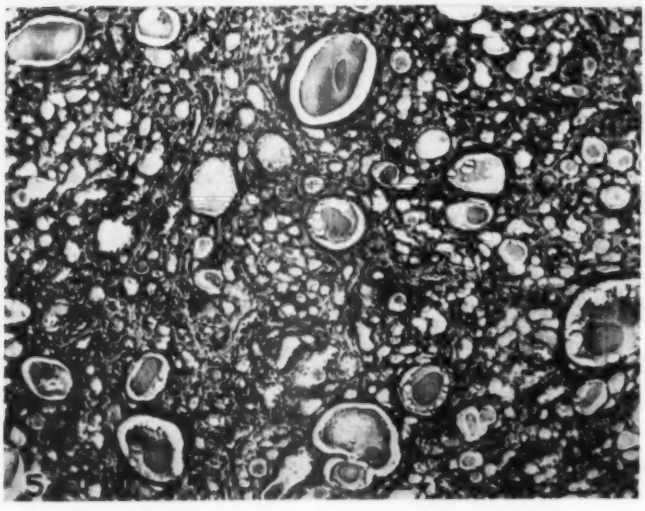


FIG. 4. SECTION FROM THYROID GLAND OF GOITROUS RABBIT (NO. 1493) SHOWING ALMOST COMPLETE INVOLUTION AFTER THE ADMINISTRATION OF IODINE FOR 8 DAYS (× 114)

FIG. 5. SECTION FROM THYROID GLAND OF GOITROUS RABBIT (NO. 1276) SHOWING PARTIAL INVOLUTION OF HYPERPLASTIC GLAND AFTER THE ADMINISTRATION OF IODINE FOR 4 DAYS (× 82)

Note the colloid which is in two concentric layers

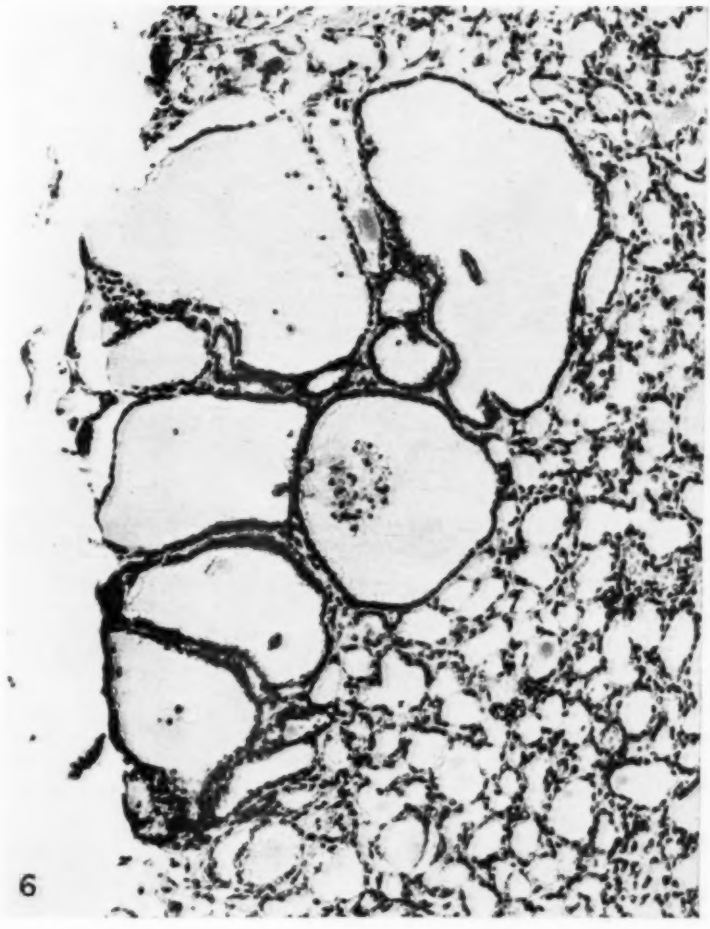
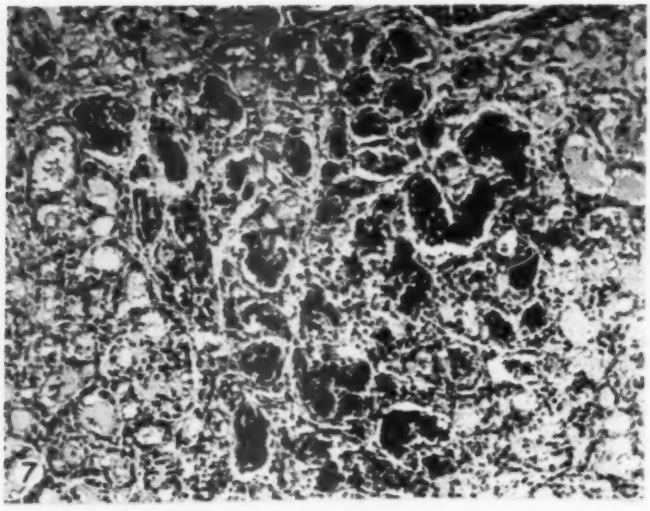


FIG. 6. (FROM RABBIT 1493). GLAND AFTER INVOLUTION FOLLOWING ADMINISTRATION OF IODINE. AREA OF HYPERINVOLUTION THAT IS BEGINNING TO BE DEMARCATED FROM THE REST OF THE GLAND



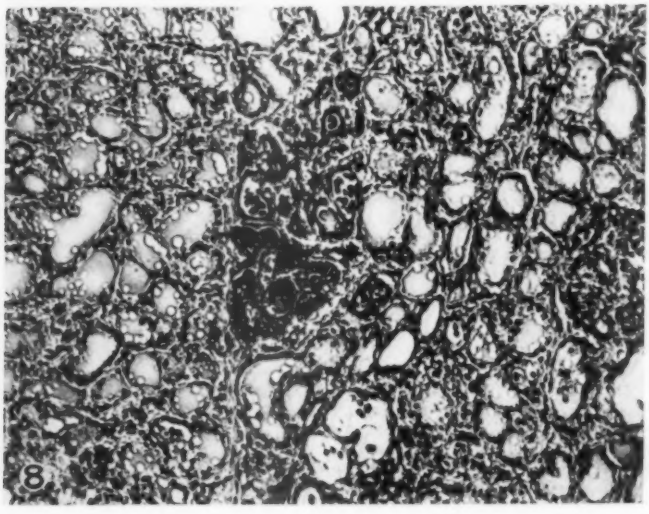


FIG. 7. (FROM RABBIT 1921). GLAND OF GOITROUS RABBIT AFTER 8 DAYS ADMINISTRATION OF IODINE (× 110)

Note the areas of persistent hyperplasia. These areas have been described by various authors as miliary or diffuse adenomata

FIG. 8. (FROM RABBIT 1921). LOCALIZED AREA OF PERSISTENT HYPERPLASIA SURROUNDED BY TISSUE IN WHICH INVOLUTION HAS OCCURRED NORMALLY IN RESPONSE TO IODINE (× 124)

response to the factors that were efficacious in bringing about involution of the remainder of the gland. They were surrounded by a local infiltration of lymphocytes. The acini were small and closely crowded together, while the lumina were filled with masses of epithelial cells. There was no colloid in these areas. This persistent hyperplasia was in some instances diffuse, resembling the miliary adenomata of other writers (Fig. 7). In other instances the process was localized and appeared encapsulated (Fig. 8). These latter areas might well be called localized adenomata.

DISCUSSION

Our observations on the effect of the administration of iodine to normal rabbits are in accord with the findings of other observers. As in the experiments of Marine, Deutch and Cipra (3), none of the animals showed marked variations in metabolism during the administration of an excess of iodine. Although our series was merely intended as a control for the goitrous animals and was too small to warrant sweeping conclusions, the results showed that in these "normal" rabbits iodine brought about an immediate but not excessive lowering of the metabolic rate with a gradual tendency to return to the normal level.

When iodine was administered to goitrous rabbits, they immediately became more alert and active. The metabolic rate rose rapidly while the body-weight fell. In most instances, death took place within a few days. Marine and Lenhart in 1909 (5) fed iodine to dogs with hyperplastic goitres and noted a decrease in body-weight. They did not carry out metabolic studies. The abrupt and marked rises in metabolism observed in our goitrous rabbits cannot be ascribed to loss of weight alone, since these animals showed increases in the total heat production. Furthermore, as pointed out in the previous paper of this series (2), losses in body-weight of animals which did not receive iodine were not accompanied by significant alterations in the metabolic rate. There can be little doubt, then, that the administration of iodine to the goitrous rabbits brought about a true increase in heat production.

These observations seem to have a definite bearing on the problems concerned with the function and pathology of the thyroid gland. The

behavior of the goitrous animals following the administration of iodine, in respect to both their general condition and their metabolism, suggested strongly that an excess of thyroid secretion had suddenly been elaborated and poured into the circulation. Marine and Williams (6) demonstrated many years ago that iodine deficiency brings about an hypertrophy of the thyroid gland. It would seem as if, in our animals, this hypertrophy had proceeded to the point where the glands were potentially able to synthesize large amounts of the thyroid secretion, if the proper elements were available. It is a well known fact that hyperplastic thyroid glands absorb iodine more readily than normal ones. The exhibition of iodine in our animals was promptly followed by symptoms and metabolic changes that could readily be ascribed to increased thyroid function. It would appear that, as soon as the deficiency of iodine was supplied, the already hypertrophied gland was able to pour an excessive amount of thyroid secretion into the blood stream. When the degree of hypertrophy was great, it is not unreasonable to suppose that the amount of secretion elaborated might well have raised the metabolism to a level which was not compatible, over any great period of time, with the life of the animal. In support of this view was our observation that the severity of the reaction following the administration of iodine was proportional to the degree of hyperplasia present in the gland.

The observations recorded in this experiment also have a bearing upon Marine's conception of the mechanism of the action of iodine in lowering the metabolic rate in Graves' disease (7). He believes that, during the process of involution, an excessive amount of colloid is laid down in the alveoli and that with this alveolar distention there is a concomitant increase in pressure upon the peri-alveolar spaces, thus blocking the absorption of thyroid secretion into the circulation. According to this conception, the lowering of the metabolic rate in hyperplastic goitre by the administration of iodine is largely the result of a mechanical process.

The results we have obtained in the normal rabbits support Marine's view, since the administration of iodine to such animals was followed by a decrease in the metabolic rate and the deposition of large amounts of colloid which so distended many of the alveoli that their epithelium was reduced almost to the pavement type. The tendency which these

animals showed toward a gradual return to a normal level of heat production would suggest that the thyroid cells slowly accommodated themselves to the increased pressure and the functional capacity of the alveolar capillaries was restored. However, the results obtained in the animals with goitre did not support this theory for, although sufficient iodine was given to bring about either partial or complete involution of the gland, there was evidence that thyroid hormone was poured into the circulation in increased amounts. It would appear that the hypothetical pressure mechanism failed to operate in the goitrous animals.

The appearance in these goitres of areas which resembled adenomata is of interest. Marine has repeatedly stated (8, 9) that adenomata have rarely been observed in the thyroid glands of animals. Rienhoff (10) has suggested that many of the so-called adenomata are brought about by the involutionary process and are in reality either colloid cysts or areas of persistent hyperplasia. Our findings indicate that similar areas can occur in animals during the process of involution of an hyperplastic goitre.

These experiments on the effect of iodine on animals with hyperplastic thyroid glands would suggest that iodine, in large doses, may prove dangerous to patients with simple, non-toxic goitres, of the iodine deficiency type. They may also explain the increase in toxic goitres noted by Hartsock (11) and others in the so-called endemic goitre belts since the introduction of iodized water and salt and the abuse of various other forms of iodine as goitre prophylactics. The production of areas resembling adenomata by the administration of iodine to animals with hyperplastic goitre suggests that the high percentage of adenomata reported by some clinics may, in part, be due to the increasing and indiscriminate popular usage of excessive amounts of iodine, both in the prevention and treatment of goitre.

SUMMARY

1. An excess of iodine in the form of Lugol's solution caused a temporary lowering of metabolic rate in six normal rabbits. There was a gradual return to the normal level.

2. Iodine, in the dosage administered, produced, in the normal

thyroid gland, a diffuse out-pouring of colloid with a flattening of the alveolar epithelium and a preponderance of the colloid cells.

3. Iodine when administered to goitrous rabbits caused a marked increase in metabolic rate, rapid emaciation and in most instances, death.

4. The severity of the reaction bore a direct relationship to the extent of hyperplasia which existed before the administration of iodine was begun.

5. Iodine tended to bring about involution of the hyperplastic thyroid gland, with a lowering of the alveolar epithelium.

6. Areas of hyperinvolution resembling colloid adenomata were observed.

7. Both diffuse and localized areas of persistent hyperplasia were noted. These resembled, respectively, the so-called miliary and small encapsulated adenomata.

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BOOK REVIEWS

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Coriat proposes to regard stammering as being due to a fixation of the libido at the oral level. He considers that the mouth subserves two purposes, the one that of ingestion, the other that of being a source of libidinous pleasure. Where there has been an intensification of that pleasure in infancy, there is more or less of a failure to pass through the usual stages of libido development, and the individual seeks to obtain pleasure by the excessive articulating movements which go with stammering. The disorder being, according to his theory, a narcissistic neurosis, he accounts for the frequent failures in treatment by psychoanalysis on the ground of the difficulty in obtaining a transference. His concept does not take care of the facts that these patients can frequently talk well when alone and can quite frequently sing faultlessly. There is an interesting description of what Coriat terms the oral erotic character, and which he believes the stammerer to share in to some degree. Quoting Abraham, he states their whole attitude towards life shows that "they expect the mother's breast to flow for them eternally." They show an overevaluation of intellectual attainments, especially in vocabulary. They are strongly narcissistic and have an attitude of omnipotence, but nevertheless carry into their adult development the lability, cheerfulness and optimism of their childhood days.

D. E. C.

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